REMARKS

Objection to the Claims

Claims 4 and 6 have been amended herein in accordance with the Examiner's recommendations. Specifically, the errant passages referring back to the V and W substituents have been removed from Claims 4 and 6. Withdrawal of the objection to Claims 4 and 6 is therefore respectfully requested.

Rejections Under §101 and §112, First Paragraph (Enablement):

Regarding the rejections under §101 and §112, first paragraph, enablement, Applicants respectfully traverse the continuance of this rejection. In particular, Applicants refer to the Examiner's comments at the bottom of page 3 of the Final Office Action. Here, in referring to Dr. Gellman's earlier Rule 132 Declaration, the Office states:

> However, nowhere in the instant specification can the examiner find any reference to blocking Bcl-x_L/BH3 domain interactions. If such a reference were present, with adequate guidance on performing such an experiment - in the instant specification, the compound would likely have utility, as blocking Bcl-x_L/BH3 domain interactions has a specific, substantial, and credible utility. Additionally, Applicants' asserted utility is not within the instant disclosure, and thus cannot provide the utility.

Applicants respectfully traverse the concluding statement in this passage on several grounds: (1) the specification as filed explicitly discusses disrupting protein-protein interactions as a useful aspect of the present invention; (2) the Gellman declaration clearly shows that the present compounds have a well-accepted utility consistent with the utility that is disclosed in the specification as filed; and (3) the '384 Patent and the Seebach et al. paper likewise are objective evidence of this well-accepted utility.

Addressing these points in order, the specification as filed is not silent with respect to utility. The specification, starting at page 19, contains an explicit discussion of the utility of the claimed compounds, a discussion that directly addresses disrupting protein-protein interactions. See also Applicants' discussion starting at the bottom of page 20 of the response filed August 4, 2005. In short, the claimed compounds are conformationally restricted, a specific structural limitation that is not shared by α-polypeptides in general. Thus, the compounds can be used "to disrupt specific protein-protein interactions," a utility explicitly articulated at page 20, third full paragraph of the specification.

Addressing the second point, Dr. Gellman's Declaration specifically discussed using a compound according to the present invention "to disrupt a specific protein-protein interaction." Thus, Dr. Gellman's Rule 132 declaration is perfectly consistent with the utility stated in the application as filed. See especially paragraph 10 *et seq.* of Dr. Gellman's Rule 132 Declaration. In short, Dr. Gellman's declaration was submitted to show that the compounds claimed can be used to disrupt a specific protein-protein interaction. The Office itself indicates in the above-quoted passage that this utility is "likely" acceptable. Insofar as the experiment described in Dr. Gellman's declaration perfectly mirrors the utility specifically mentioned in the specification as filed, Applicants submit that the rejection under §§101 and 112, first paragraph (enablement) are improper and should be withdrawn.

Regarding Applicants earlier submission of U.S. Patent No. 6,958,384 for the Examiner's consideration, this patent was submitted solely as a piece of objective evidence to show that **contemporaneous** applications that issued as patents articulated the **same** utility as asserted in the present application. In other words, Applicants were not (and are not) asking the Office to pass judgment on the utility or operability of the invention claimed in the '384 Patent. The specification of the '384 Patent is presumed to satisfy the utility and enablement requirements. What Applicants are asking the Office to do is to weigh the '384 Patent (as well as the Seebach et al. paper) as **objective evidence** of a well-established utility for the presently claimed compounds. As noted in Applicants' earlier responses, an application as filed does **not** have to contain any statement of utility if the claimed invention has a well-established, specific, substantial, and credible utility. As also noted earlier, Applicants are allowed to submit objective evidence to show the existence of a well-established utility (and the Office is duty bound to consider that evidence). *See* MPEP §2107.01(II).

Both the '384 Patent and the earlier-submitted Seebach et al. paper are objective evidence that establish that the presently claimed compounds have a well-established utility. And Dr. Gellman's declaration clearly establishes that a person of ordinary skill in the art is well aware of that same utility, namely disrupting specific protein-protein interactions.

Backtracking slightly, the application that matured into the '384 Patent was published on November 13, 2003 (less than three months after the filing date of the present application). The '384

Patent is therefore **contemporaneous** in time with the present application. And, as noted earlier, the utility articulated in the '384 Patent is **identical** to the utility recited in the current application. For example, see the '384 Patent at col. 12, lines 5-40 and compare it to the passage starting at page 19 of the present application. Again, Applicants are not asking the Office to pass judgment on the '384 Patent. The '384 Patent has an acceptable utility. But the Office must consider as objective evidence of a well-understood utility **for the presently claimed compounds** that the utility articulated in the '384 patent **is identical** to the utility recited in the current application. Thus a person of ordinary skill in the art would invariably grasp that the well-understood utility articulated in the '384 Patent is also shared by the presently claimed compounds. Applicants respectfully assert that the '384 Patent, coupled with the Seebach et al. paper, and Dr. Gellman's 132 declaration, do establish that the present claims have a well-established utility as per MPEP §2107, as well as a specifically articulated, substantial, credible, and tangible utility.

Regarding the references cited in rebuttal by the Office, Applicants respectfully note that the Office has admitted on the record that the Schmitt et al. paper (cited at page 6 of the Final Office Action) **is not** contemporaneous in time with the present application. Thus, the Schmitt et al paper is not probative on the question of utility.

Regarding the Kim et al. reference (more of which below) Applicants note that the utility articulated in the Kim reference (cited by the Office at page 5 of the Final Office Action) **is not** the same utility as articulated in the present application. Kim et al. looks solely at the ability of the β-Pro decamer **to bind** to profilin. That is, Kim et al. were aiming to create a ligand for profilin - a very specific utility. And a utility that is distinct from disrupting the interaction of profilin with its α-polypeptide binding partner. The specific β-Pro decamer tested by Kim et al. did not itself bind to profilin. But notably, Kim et al. did not do any competitive testing in which profilin was simultaneously exposed to both the α-proline analog and the β-proline analog. Kim et al. found that the β-proline analog was not a ligand for profilin, but are notably silent on whether the β-proline analog antagonizes or otherwise disrupts the binding of the α-proline decamer. The paragraph starting at page 19, line 19 of the present specification, notes that "The effect the compound [i.e., the claimed compounds] has on

any given reaction provides valuable information on either or both of the kinetics and/or the thermodynamics of the reaction being studied." But Kim et al. **did not** use the β-proline decamer to study the interaction of the profilin with the α-proline decamer; Kim et al. were trying to see if the β-proline decamer itself would act as a ligand for profilin. This is a different and distinct utility from the utility articulated at page 19 of the specification. Thus, the Kim et al. paper is not probative on the matter of utility because it looks at a distinct utility from that disclosed in the present application.

Applicants also again point out that the specification is not silent with respect to the specific, substantial, and credible utility required by MPEP §2107(II). (This section of the MPEP dictates that an invention has a well-established utility if: (i) a person of ordinary skill in the art would immediately appreciate *why* the invention is useful based on the characteristics of the invention (*e.g.*, properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.) The utility explicitly discussed in the specification as filed is backed by Dr. Gellman's Rule 132 declaration, which directly addresses the utility disclosed in the application as filed and shows that these compounds can be used to disrupt specific protein-protein interactions.

Applicants thus submit that the rejections under §101 and 112, first paragraph (enablement) are untenable. Withdrawal of the rejections are respectfully requested.

Rejection of Claims 4 and 6 Under §112, First Paragraph (Written Description):

This rejection is believed to have been overcome by appropriate amendment to the claims. Specifically, the phrase noting that R^{15} and R^{16} cannot simultaneously be hydrogen has been removed from the claims. The definition of R^9 has been culled from the definition of R^{10} and R^{13} and modified consistent with the recitation contained in the original Markush group definition for R^9. Hydrogen is no longer a possible substituent for R^9.

Applicants respectfully submit that substituents now recited for R^9 enjoy verbatim support in the specification and claims as originally filed. See, for example, page 13, in the paragraph beginning at line 10. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 4 and 6 Under §112, Second Paragraph:

This rejection is believed to have been overcome by appropriate amendment to the claims. The offending phrase "comprise," as highlighted by the Office at page 10 of the Final Office Action has been replaced with the definite phrase "is," Thus, for example, Claim 4 now reads, in relevant part, that "at least one X or Z **is** an α-amino acid residue and at least another two of X or Z **are** two cyclically-constrained β-amino acid residues." Claim 6 has been amended in an analogous fashion.

Applicants believe that this change directly addresses the issue raised at the bottom of page 10 of the Final Office Action. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 4 and 6 Under §102(a) Over Kim et al.:

This rejection is believed to have been overcome by appropriate amendment to the claims. Specifically, the definition of R9 in the present claims has been amended to exclude from the scope of the claims the $(\beta\text{-Pro})_{10}$-α-Tyr compound described in Kim et al.

Withdrawal of the rejection is respectfully requested.

CONCLUSION

In light of the above amendment and remarks, Applicants submit that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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